

16 September 2008

The Honorable John D Dingell & Bart Stupak
Chairmen, US House of Representatives
Committee on Energy and Commerce &
Subcommittee on Oversight & Investigations
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Dear Mr Dingell and Mr Stupak

Response to your letters about our work on ezetimibe (dated 21 August & 2 September: copies attached)

As many of the questions in your letters about our ezetimibe analyses can best be answered directly by the CTSU, I am sending you our responses to them as an Annex to this letter (with copies to the NEJM and the companies concerned), and am making the whole correspondence publicly available on www.ctsu.ox.ac.uk.

In July 2008, acting under their own initiative, the academic investigators of the main ezetimibe trials rapidly organised an international meta-analysis of all the available data on cancer rates. They reported preliminary results within 1 week that were sent immediately to the FDA (and made public at a press conference the same day, 21 July) and published final results within 7 weeks (NEJM, 2 September). The main conclusion was that the trial results provide “no credible evidence” that ezetimibe affects cancer rates.

All relevant conflicts of interest were declared, but are of no material relevance to the reliability of this conclusion, for any competent trial statistician would endorse it (as long as, in examining the data, an appropriate distinction is made between the original trial result that unexpectedly generated concern and the other trial results that provide an independent test of that concern).

Sequence of events

One ezetimibe trial (SEAS) ended this year, and two more (SHARP and IMPROVE-IT) are still in progress, one of which (SHARP) is being conducted here at the University of Oxford, independently of the pharmaceutical companies (Merck/Schering-Plough) that are funding it. In mid-July, the SHARP and IMPROVE-IT investigators were told by the companies of an apparent excess of cancer in the then-unpublished SEAS trial results. These two groups of investigators were, of course, both blind to their own interim results, but knew that their two trials together involved substantial numbers of patients.

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Hence, to help check whether there was any real hazard, the SHARP and IMPROVE-IT investigators decided to ask their Data and Safety Monitoring Committees (DSMCs) to allow independent analyses of the cancer data from all three trials (with SHARP and IMPROVE-IT combined), the findings to be reported simultaneously to the DSMCs, the FDA and other regulatory authorities and the companies. Both DSMCs agreed to this, as did the SEAS investigators, and Professor Rory Collins (Chair of the SHARP Steering Committee) obtained the data and asked me – as statistician to the SHARP DMC, and as a cancer epidemiologist – to lead the analyses and their interpretation.

The companies were told what was being done, but did not know the results or receive any draft of my report before it was finalised and sent out by email to FDA and others on 21 July 2008. Knowing when my report would be sent to FDA (but not what it would contain), the companies arranged beforehand that a televised press conference would take place later on 21 July that would give journalists the results directly and let them question me freely.

Professor Collins then suggested (again independently of the companies) that we should rapidly prepare a fuller report of the findings for submission to the New England Journal of Medicine, and peer-reviewed online publication of it (involving slightly updated data) took place on 2 September as **Peto R et al “Analyses of Cancer Data from Three Ezetimibe Trials.”** *NEJM* 2008: 359 (10.1056/NEJMsa0806603). That NEJM publication, which includes a declaration of all relevant interests, should answer all your concerns. Its main conclusion is that *“the available results from the three trials do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer.”*

In addition, the SHARP and IMPROVE-IT DSMCs (who also have access to interim results on other outcomes) have recommended that those trials continue. As noted in our NEJM report, their continuation will permit even more reliable evidence to emerge about the effects of combined ezetimibe and statin therapy (which produces a larger reduction in LDL cholesterol than can be achieved by monotherapy), not only on cancer but also – and, perhaps, most important – on the heart attacks, strokes, and other major vascular outcomes that such treatment may be found to prevent.

It is not in the interests of public health to label potentially useful drugs as unsafe if there is no credible evidence that they are – or, of course, to overlook reliable evidence of hazard if it does emerge. In trying to avoid both of these errors, the best thing is for unexpected findings (like the apparent excess risk of cancer in the SEAS trial) that generate but do not prove the hypothesis of a new hazard to be tested by a separate analysis of an independent, substantial set of data when monitoring the safety of potentially important drugs.

Yours sincerely,



Sir Richard Peto, FRS
Professor of Medical Statistics
and Epidemiology

PS Request that your subcommittee declare its own potential conflict of interest:

Twenty academic co-authors published a careful critique of your subcommittee's investigation of the breast cancer researcher Dr Bernard Fisher in the 1990s. (Peto R et al. The Trials of Dr Bernard Fisher: A European perspective on an American episode. *Controlled Clinical Trials* 1997; 18: 1-13; one of the sections is entitled "*Inappropriate congressional subcommittee procedures*": see attached article.) Given this, it might well be appropriate for you and any of your subcommittee members or staff to describe this potential conflict of interest when commenting directly or indirectly on the CTSU's work.

Annex: Responses to numbered points in your letters of 21 August and 2 September

Attached: 1997 article from *Controlled Clinical Trials*

ANNEX: Responses from the Clinical Trial Service Unit (“CTSU”) to numbered questions in 21 August and 2 September letters from Mr Dingell and Mr Stupak

Letter of 21 August 2008; four numbered questions:

Question 1: “How much is Dr. Peto and his institute, the Clinical Trial[s] Service Unit of Oxford University, being paid directly or indirectly by Merck, Schering-Plough, the joint venture, or their agents, attorneys, or lobbyists to conduct the SHARP trial?”

Answer: The Clinical Trial Service Unit (CTSU) is co-directed by Professor Richard Peto, who is a statistician, and by Professor Rory Collins, who is a medical doctor. Their salaries are not directly or indirectly paid for by industry or by industry-sponsored projects. Moreover, the CTSU has a staff policy of not accepting any honoraria, consultancy fees or other payments directly or indirectly from industry, as indicated in our 21 July press release, our 2 September NEJM report and our website www.cstu.ox.ac.uk. (Where appropriate, however, the costs of travel and accommodation for attending scientific meetings can be reimbursed.)

All CTSU grants from industry are administered by Oxford University, and the CTSU conducts, analyses and interprets the studies independently of industry (with the datasets held by the CTSU rather than the companies). The research grant from Merck/Schering for the Study of Heart and Renal Protection (SHARP) was about £35M, to be paid over the period 2001-9. Since 1997, Merck has also provided grants for three other major independent CTSU trials, the Heart Protection Study (HPS, 1993-2007), the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH, 1997-2009) and Treatment of HDL to Reduce the Incidence of Vascular Events (THRIVE/HPS-2, 2005-13) plus genetic analyses of stored samples from those trials, which total about £70M. (Please note that these figures from the University accounting system are in UK currency, and UK/US exchange rates have varied.) All of these studies resulted from research initiatives undertaken by the CTSU for public health reasons.

Question 2: “Which data referenced above (SEAS or CTSU) are the correct data from which health care providers should base their clinical judgment?”

Answer: Neither: your question is just about the SEAS cancer results but, as stated in our NEJM report (10.1056/NEJMsa0806603), if clinicians want their clinical judgement to be informed by the currently available trial evidence on whether ezetimibe causes cancer, then they should chiefly use not the hypothesis-generating SEAS results, but the hypothesis-testing results just from the other two trials (in which 313 ezetimibe-allocated and 326 control-allocated patients developed cancer, risk ratio 0.96). As for the detail of the SEAS cancer results, the slight discrepancy between the SEAS and CTSU 21 July press releases arose because the SEAS investigators had been analysing the numbers of “serious adverse events” that had been recorded, and 11 cancers that had arisen more than 15 days after the trial treatment (active or placebo) ended had, in accordance with standard procedures, not been recorded as “serious adverse events”. As explained on page 3 of our 21 July report to FDA (and at the 21 July press conference), the CTSU analyses did include these 11 extra cancers. Subsequent review of the cancer data resulted in some small further changes which are described, along with finalised numbers, in our 2 September 2008 NEJM report (10.1056/NEJMsa0806603).

Question 3: “What are the complete data for the number of randomized patients, as well as the number of cancers and cancer deaths, in each treatment arm of the SEAS, SHARP, and IMPROVE-IT trials?”

Answer: These numbers (with SHARP and IMPROVE-IT combined, as was required by their DSMCs) are provided in the reports published in the NEJM on 2 September 2008.

Question 4: “Upon completion of the SHARP and IMPROVE-IT trials, will Merck, Schering-Plough, or its joint venture, conduct another full analysis of the relationship between Vytorin and cancer and cancer deaths based upon complete versus preliminary data?”

Answer: On completion of the SHARP trial, its analysis will be conducted independently by the CTSU who hold the database (and not by the companies). As with the present combined analysis of the interim data, the CTSU intends to conduct, in collaboration with the research team from IMPROVE-IT, an independent meta-analysis of the final cancer data from SHARP and IMPROVE-IT (along with those from any other relevant trials then available).

Letter of 21 August 2008; four numbered requests:

“Please provide all records since 1 January 1998 relating to the following:

1. *“All payments by Merck, Schering-Plough, the joint venture, or any of their agents, attorneys, or lobbyists to Dr. Peto or the Oxford University Clinical Trial[s] Service Unit for any work related to Vytorin or for any other reason;*
2. *“Any and all contracts or agreements between Merck, Schering-Plough, or the joint venture and Dr. Peto or the Oxford University Clinical Trial[s] Service Unit for any work related to Vytorin or for any other reason;*
3. *“All communications between Merck, Schering-Plough, or the joint venture and Dr. Peto or the Oxford University Clinical Trial[s] Service Unit; and*
4. *“All communications between Merck, Schering-Plough, the joint venture, or any of their agents, attorneys, or lobbyists and any Government officials related to the SHARP, IMPROVE-IT studies, or any work done by or on behalf of Dr. Peto or the Oxford University’ Clinical Trial[s] Service Unit or any of their agents or contractors.”*

It is for the companies to decide how to deal with these four requests for various records since 1 January 1998. Providing copies of all communications (requests 3 and 4) would, however, involve an unreasonably vast amount of effort, as CTSU has over a period of more than 10 years been conducting four major independent trials of Merck’s cholesterol-modifying drugs on about 60,000 patients, each involving extensive correspondence. Such requests seem to constitute inappropriate harassment, if the term “records” is defined as widely as in the attachment to your letter of 21 August. For, as noted in our covering letter, the key scientific points that our reports make would be self-evidently true to any competent statistician who, in examining the data, distinguishes appropriately between the hypothesis-generating data set and the hypothesis-testing data set.

Letter of 2 September 2008; seven numbered questions:

Question 1: “Is the attached report the totality of Dr Peto’s submission to FDA?”

Answer: Yes: there is no “secret report” to FDA or anyone else.

Question 2: “Why was Dr. Peto’s consultant study not made publicly available?”

Answer: This is not a “consultant study”; Professor Peto is not paid by anybody as a “consultant”. On 21 July 2008, his report was provided by the CTSU to FDA and other regulatory authorities to help the regulators carry out their pharmacovigilance functions, and later that afternoon the CTSU made the results publicly available by means of a press release and press conference (as noted in paragraph 2 of your letter of 2 September 2008). The CTSU has since published updated versions of the results in a peer-reviewed NEJM report.

Question: “When did Merck, Schering-Plough, the Merck/Schering-Plough joint venture, or any of their agents, attorneys, or lobbyists first contact Dr. Peto about his consultant report?”

Answer: Again, it is not a “consultant report”. Professor Rory Collins asked Professor Peto, independently of the companies, to undertake it. Merck had contacted Professor Collins (as chair of the SHARP trial Steering Committee) about the SEAS results on Tuesday 15 July. Without knowledge of the unblinded results in either SHARP or IMPROVE-IT, Professor Collins proposed that the cancer data from SEAS, SHARP and IMPROVE-IT be sought in confidence by CTSU for an independent analysis in which the SHARP and IMPROVE-IT results would not be separately identifiable. Professor Collins then obtained agreement for this initiative from the chair of the SHARP trial Data Monitoring Committee (Professor Peter Sandercock), the SEAS trial principal investigator (Professor Terje Pedersen), the co-chairs of the IMPROVE-IT trial Steering Committee (Professors Eugene Braunwald and Robert Califf) and the chair of the IMPROVE-IT trial Data Monitoring Committee (Professor Scott Grundy). Professor Collins (with colleagues in CTSU) coordinated the liaison with the SEAS and IMPROVE-IT investigators, as well as with Merck/Schering-Plough, to obtain the unblinded cancer data from these trials.

Question 4: “When was Dr. Peto’s report submitted to FDA?”

Answer: The CTSU provided its independent report directly to the FDA and to the European drug regulatory authority on Monday 21 July 2008 (and, at the same time, copied it to Merck and Schering-Plough for circulation to other regulatory authorities worldwide, and to the principal investigators and Data Monitoring Committee chairs of the three trials). A few hours later, the CTSU described the findings fully at a 2-hour international press conference, where journalists were free to ask questions.

Question 5: “Was Dr. Peto’s report reviewed or edited prior to its submission to FDA by anyone from Merck, Schering-Plough, the Merck/Schering-Plough joint venture, or any of their agents, attorneys, or lobbyists? Please supply any drafts and all other documents that describe the review or editing of the report.”

Answer: No; the CTSU did not provide any advance drafts of its report to Merck, Schering-Plough, the Merck/Schering-Plough joint venture or any of their agents, attorneys, or lobbyists.

Question 6: “Has Dr. Peto prepared any other analysis of the association (or lack thereof) between Vytorin and cancer for any other regulatory agency or peer-review journal?”

Answer: Yes; a more detailed report was, at Professor Collins’ suggestion, prepared after 21 July, which was peer-reviewed and published on 2 September 2008 in the New England Journal of Medicine: Peto R et al. Analyses of Cancer Data from Three Ezetimibe Trials. *NEJM* 2008; 359 (10.1056/NEJMsa0806603). As with the preliminary report that had been submitted to regulatory authorities on 21 July 2008 (see response to question 5), the CTSU did not provide the companies or their agents with any advance drafts of the NEJM paper.

Question 7: “What role, if any, did Merck, Schering-Plough, the Merck/Schering-Plough joint venture, or any of their agents, attorneys, or lobbyists have in the preparation of the attached Peto report and decision to submit it to FDA?”

Answer: The preliminary report for FDA and other regulatory authorities was initiated by Professor Rory Collins in the CTSU, blind to the interim results from SHARP or IMPROVE-IT, and (as indicated above) the analyses and their interpretation were conducted independently within the CTSU. Merck, Schering-Plough and the Merck/Schering-Plough joint venture, along with the IMPROVE-IT and SEAS investigators, helped to ensure that cancer data provided to the CTSU for these independent analyses were as accurate and as complete as possible given the expedited timelines, but did not know the results or the interpretation of them until the report had been sent to the FDA. Professor Collins was responsible for the decision to prepare and submit a fuller report for peer-reviewed publication in the NEJM, and Professor Peto and others in the CTSU led the preparation of that report, in collaboration with the other co-authors (but not the companies or their agents).

Letter of 2 September 2008; demand for staff interview:

“Finally, we ask that you make Dr. Peto available for a staff interview as soon as possible.”

Answer: The companies are not in a position to make Professor Peto available since he is a tenured professor at Oxford University, and companies have no control over him. (Moreover, as described on our website, the CTSU has a policy of taking no honoraria or consultancy fees from industry.) If, however, you, your staff or subcommittee would like to invite Professor Peto’s assistance as an epidemiologist in seeking statistically appropriate ways of interpreting the hypothesis-generating and hypothesis-testing data sets from trials in general, and from these three trials in particular, he would be happy to try to help.

[end of Annex]